An Improved Approach to Assessing the Inhalation Risk of Chloroform

JC Lipscomb, US EPA/ORD/NCEA, Cincinnati, OH
Gregory Kedderis, Independent Consultant, Chapel Hill, NC

Chloroform is a drinking water disinfectant byproduct and is a potential health concern because excess exposure damages the liver and kidney. Exposure from drinking water occurs via the oral, dermal and inhalation routes. Oxidative metabolism of chloroform in the liver is catalyzed by cytochrome P450 2E1 (CYP2E1) and produces phosgene and HCl which, at high concentrations, lead to cytolethality, subsequent cell proliferation or hyperplasia and cancer; chloroform is not thought to be carcinogenic in the absence of cytolethality. The content of CYP2E1 varies among the humans, influenced by ethanol ingestion, stress, fasting, genetics and diabetes. The delivery of chloroform to the liver by hepatic blood flow is also a determinant of metabolism; hepatic blood flow varies among humans. For systemic toxicity, data from rodent studies indicate that 5 ppm may be a safe exposure level. While rodents develop nasal toxicity at lower concentrations, the effect is not seen in humans, and species differences in the distribution of enzymes to nasal tissues may be partly responsible. Chloroform's RfC will be developed based on systemic effects and the approach employs physiologically based pharmacokinetic modeling to transition concentrations of chloroform in inspired air to amount of metabolite formed in the liver of adults and children. The model is improved over predecessors including measures of variability in CYP2E1 content derived from human adult and child organ donor tissues, the biochemically-measured specific activity of human CYP2E1 toward chloroform, clinically-derived measures of variability in hepatic blood flow (% of cardiac output) among humans, and the blood:air partition coefficients derived from human adult and child blood. The results quantify animal-to-human and human interindividual variations in the risk relevant pharmacokinetic outcome, which can replace default uncertainty factors with scientifically-defensible numerical estimates of variability across and among species.

CHLOROFORM: Inhalation Risk Assessment, Drinking Water Contaminant

Exposure and Site of Toxicity
- Drinking Water Disinfection Byproduct
- Highly Volatile
- Indoor Air Contaminant
- Enters Blood from Inhaled Air
- Metabolized in Liver to Become Toxic
- Liver Toxicant

Risk Assessment Application
Refine and employ physiologically based pharmacokinetic (PBPK) modeling to aid extrapolation of toxicity findings from animals to humans and among humans; use toxicity mode of action information to develop model structure

Physiologically Based Pharmacokinetic (PBPK) Modeling
- Simultaneous Ordinary Differential Equations
- Parameter Values Determined for this Application
- Addresses Liver Metabolites in:
  - Rats
  - Mice
  - Adult humans
  - Children

Animal Studies and Extrapolation to Humans
What human exposure produces the same level of CF metabolite as observed in the mouse at the no-effect level?

Many inhalation studies with rats and mice
- Human epidemiology studies Do Not indicate nasal effects
  - Liver is the most sensitive organ
  - Mice are more sensitive than rats

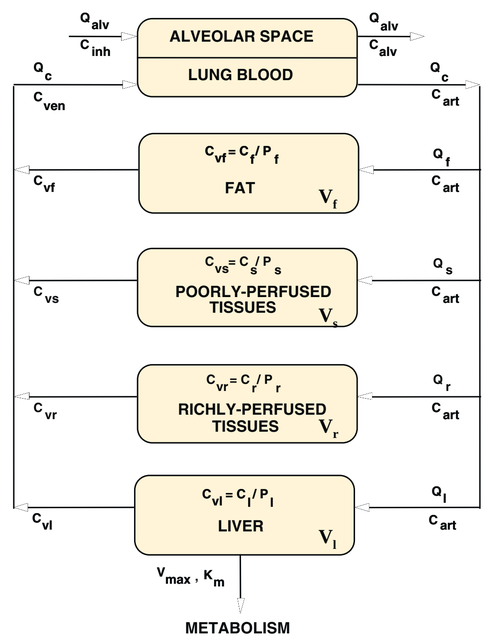
Human Variability
When the level of CF metabolite is held constant and blood solubility, liver blood flow and liver metabolism are varied in adults and children, how different are the exposure concentrations?

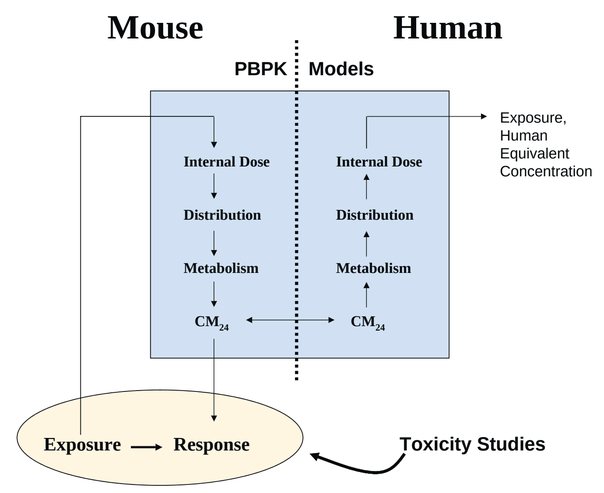
Apply PBPK Modeling
Identify important parameters which vary
- Blood Solubility - Determined from the laboratory
- Liver Blood Flow - Determined from the literature
- Metabolism - Determined from the laboratory

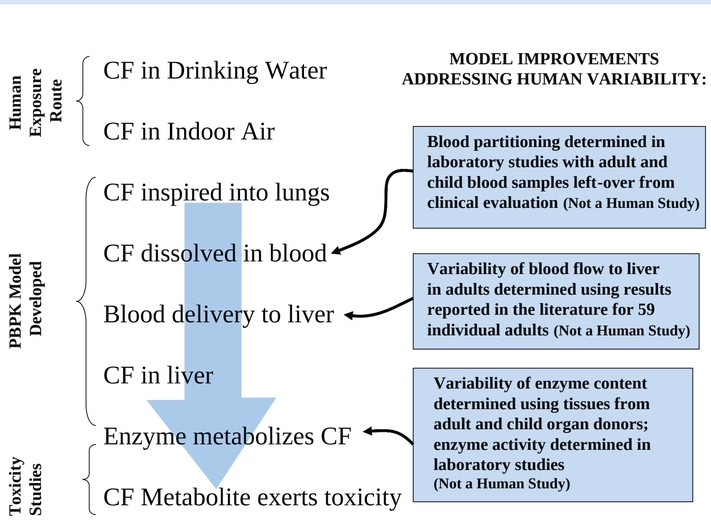
Considering Children
- They are not scaled-down adults
- They are not scaled-up animals
- Use age-specific organ sizes and blood flow patterns
- Develop and use data on enzyme content for metabolism
- Develop PBPK model for neonates (1 yr) and juveniles (9 yr)
- Neonate is 10 kg; Juvenile is 30 kg - tied to water regulations

Supported by Additional Collaborations
- US EPA/ORD/NHEERL
- US EPA/ORD/NERL
- Centers for Disease Control and Prevention / National Institute for Occupational Safety and Health
- U.S. Air Force Research Laboratory

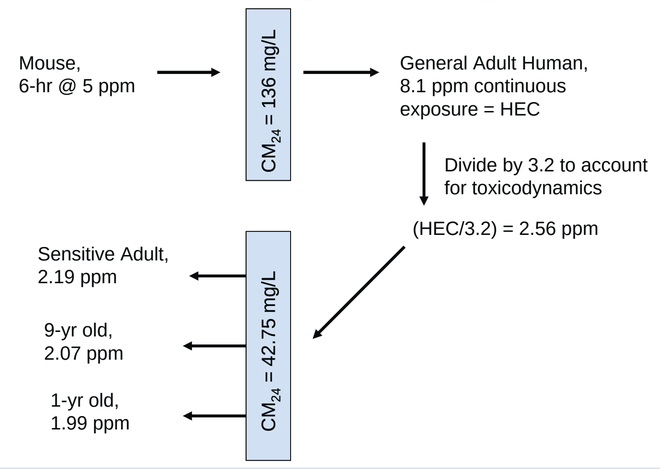
Schematic of PBPK MODEL







Inter- and Intraspecies Extrapolation



Conclusions:

- We used PBPK modeling to extrapolate risk-important tissue doses of toxic metabolites between mice and humans.
- We determined which physiologic factors (blood solubility, liver blood flow, liver metabolism) most limited chloroform metabolism and quantified their natural variations in adults and children, employing Agency-conducted and Agency-led research in the process.
- We relied on Agency guidelines and Agency precedent to extrapolate from animals to humans.
- There isn't any Agency guidance on exactly how to address human variability for risk assessment; our practice is based on recommendations, international precedent and application of scientific principles.
- From the available information, it seems children are not dramatically different from adults in the way chloroform is metabolized in the liver.
- Quantitative reliance on these results may support replacement of the default uncertainty factor values resulting in an inhalation RfC for chloroform as high as 0.6 ppm (i.e., (8.1 ppm HEC/3.16]/[1.3 × 3.16] = 0.62 ppm).

Important Reference Materials:

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